		gn (+) inside this			1	PE CO	-Approved	PTO/SB/08A for use through 10/31/2002. OMB 06 Office: U.S. DEPARTMENT OF COM unless it contains a yalid OMB-control	51-063 IMERISE number
Under th	Substitute INFO STA	e for form 1449A  ORMATIC  TEMEN  (use as many	NPTO ON DIS T BY A	SCLO APPLI	SURE CANT	Application Filing Date First Name Group Art L Examiner N	Number ed Inventor	nplete if Known 09/997, 490 17 Nov 2001 XIND NBSS	
フ.	Sheet	1	of	2		Attorney Do	ocket Number		_8/
_					U.S. PA	TENT DOCUM	MENTS		

				U.S. PATENT DOCL	IMENTS	
Examiner Initials	Cite No.1	U.S. Pater Number	Kind Code <sup>2</sup>	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
0		5,912,2		ombardelli et al	06/15/1999	text w/o figure text w/o figure
a		6.218.3	169	Bombardelli et al	04/17/2001	fext W/O Tigure
		-				
	-	-				
	+-	1				
	1					
<b> </b>	+	<del></del>				

				FORE	IGN PATENT DOCUMENT	rs		
		F	oreign Patent Do		Name of Patentee or	Date of Publication of Cited Document	Pages, Columns, Lines, Where Relevant	
Examiner Initials	Cite No.1	Office <sup>3</sup>	Number <sup>4</sup>	(If known)	Applicant of Cited Document	MM-DD-YYYY	Passages or Relevant Figures Appear	T6
								—
		<del>                                     </del>						┷
	<del> </del>	<del>                                     </del>						4-
	<del> </del>	1-1-						- -
		1 1						- -
	1	1						╫
	1							┿
		1-1-						
	$\vdash$	1					<u></u>	

Examiner Signature	Date 3/18/03
Cignostic V C	the state of the state of the conformance and

\*EXAMINER: Initial If reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>6</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U. S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

	卫
	M
	$\mathbf{C}$
	Ш
	7
3	$\overline{\mathbb{H}}$
J	Ü

	us sign (+) inside this		→□ [震	2 6 2(	Approve	PTO/SB/08B ed for use through 10/31/2002. OMB 0 ark Office: U.S. DEPARTMENT OF CO n unless it contains a valid OMB control	651-13031 MMERGE	+mAY	REC
	ite for form 1449B/PT(			HADEN	Cor	mplete if Known	THE	0	m
				ne l	Application Number	09/947440	型	တ	
INFO	ORMATION	N L	ISCLOSU	KE	Filing Date	[ 17 Nov 2001	த	25	
STA	TEMENT	RY	APPI ICA	NT	First Named Inventor	KINDNESS	ല	2002	Ш
017		<b>-</b> .	, , L ,	•	Group Art Unit	16/9	12		
1	(use as many s	sheet	s as necessary)		Examiner Name		1600/2900		
Sheet	2	of	2		Attorney Docket Number		رو		

	_	OTHER PRIOR ART -	- NON PA	TENT LITERA	TURE	E D	OCL	JME	ENTS	3				
Examiner Initials	Cite No.1	Include name of the author (in CAF	PITAL LETTI	ERS), title of the art	ticle (wi	hen (s),	appro	pria	te), tit	le of	the er(s),			T <sup>2</sup>
		Please see attached	pages	numbered	as	1	of	9	to	9	of	9		
					·								-	
				-						7				
											-	-		
			•		· ·									
			····											
Examir Signat						Dat Cor	e nside	red	T	<del></del>				

<sup>&</sup>quot;EXAMINER: Initial If reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>&</sup>lt;sup>1</sup> Unique citation designation number. <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached.

OTHER PRIOR

Sheet 1 of 9

APR 2 6 2002

AY 0 3 21 DENEER 16

Group Art Unit:\_

Examiner Name: Atty. Docket No.

PATENT LITERATURE DOCUMENTS

					1
-	Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	ΙT	ı
1	Exammer			1	1
	Y 142 - 1 -	MI.	city and /or country where published	İ	ı
	Initials	No.	•	Ь	J

G	MASFERRER JL et al, "Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors," Cancer Research 60(5): 1306-11, March 1, 2000.	
	RUI YC, "Advances in pharmacological studies of silymarin," Mem. Inst. Oswaldo Cruz, Rio De Janeiro, Vol. 86 Suppl. II, 79-85, 1991.	
	ZI X, "A flavonoid antioxidant, silymarin, inhibits activation of erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1 arrest, and anticarcinogenic effects in human prostate carcinoma DU145 cells," Cancer Research, 58(9):1920-29 May 1, 1998.	
	HEBER, D. et al, "Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement", Am. J. Clin. Nutr. 69: 231-36 (Amer. Socy. For Clin. Nutrition) 1999.	
	HONG SH et al, "Relationship of arachidonic acid metabolizing enzyme expression in epithelial cancer cell lines to the growth effect of selective biochemical inhibitors," Cancer Research 59:2223-28, May 1, 1999.	
	SPARROW C. et al, "Simvastatin has anti-inflammatory and antiatherosclerotic activities independent of plasma cholesterol lowering," Arterioscler. Thromb. Vasc Biol. 21(1): 115-21 (Jan. 2001) (Amer. Heart Assoc. 2001).	
	WILSON, S., et al, "Simvastatin Preserves Coronary Endothelial Function in Hypercholesterolemia in the Absence of Lipid Lowering," Arterioscler Thromb Vasc Biol. 2001;21:122-128 (January, 2001) (Amer. Heart Assoc. 2001)	
7	DEHMLOW C, et al, "Scavenging of reactive oxygen species and inhibition of arachidonic acid metabolism by silibinin in human cells," Life Science 58(18): 1591-1600 (Elsevier 1996).	
R	ZHAO J et al, "Significant inhibition by the flavonoid antioxidant silymarin against 12-O-tetradeconoylphorbol-13-acetate-caused modulation of antioxidant and inflammatory enzymes, and cyclooxygenase 2 and interleukin-1 alpha expression in SENCAR mouse epidermis: implications in the prevention of stage I tumor	

		2			
Examiner signature	1	2	7	$\overline{\mathcal{V}}$	Ĺ
			:		$\overline{}$

APR 2 6 2002

Sheet 2 of 9

Appl. No.\_ 0 9 / 94 Filing Date First Named Inventor: Kindness

Group Art Unit: Examiner Name: Atty. Docket No.

PATENT LITERATURE DOCUMENTS OTHER PRIO

			an
T	Cita	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	1
Examiner	Cite	Addition in Califfab Editates, and states,	1
I .	•	city and /or country where published	1
Initials	l No.	City and for country where published	l .
Linuais	110.		

0	promotion," Molecular Carcinogenesis, 26:321-333 (Wiley-Liss, Inc. 1999).	
<del>  /,   -</del>	GRAF, B., et al., "Proinflammatory Signals Upregulate COX-2 and	
/	Increase PGE2 Production in Biphenotypic B/Macrophage Cells,"	
	Annuals New York Academy of Sciences 905:294-296, April, 2000	ı
	(NY Acad. Of Sci 1999).	
<del></del>	TO, K.F., CHAN, K.L., et al., "Up-regulation of cyclooxygenase-1	
	and -2 in human gastric ulcer," Aliment Pharmacol Ther 2001:	
\	15:25-34, September, 2000 (Blackwell Science Ltd. 2001).	1
<del></del>	CHONG, R. Y., et al., "Efficacy of parenteral methotrexate in	
	refractory Crohn's disease," Aliment Pharmacol Ther 2001: 15:35-	j
	44, September 11, 2000 (Blackwell Science Ltd. 2001).  BUTTAR, et al., "The "Aspirin" of the New Millennium:	
	BUTTAK, et al., The Aspirili of the New Miniciality.	
	Cyclooxygenase-2 Inhibitors," Mayo Clinic Proceedings, 75(10):	
1 1 1	1027-1038, October 2000, (Mayo Foundation for Medical Education	
	and Research 2000).	
	NIE, D., "Eicosanoid Regulation of Angiogenesis in Human	
1 1 1	Prostate Carcinoma and Its Therapeutic Implications," Annals New	
	York Academy of Sciences, 95: 165-176, April, 2000 (NY Acad. Of	
	Sci. 2000).	
	JAULIN, N., "Reduction of the Uptake by a Macrophagic Cell Line	
	of Nanoparticles Bearing Heparin or Dextran Covalently Bound to	
	Poly (methyl methacrylate)," Journal of Drug Targeting, 2000, 8(3):	
	165-172 (Overseas Publishers Assocation N.V.2000) (Abstract).	-
	GUPTA, R.A., et al., "Translational Studies on Cox-2 Inhibitors in	
	the Prevention and Treatment of Colon Cancer," Annals New York	
	Academy of Sciences, 910:196-206 (NYU Acad. Of Sci. 2000).	<u> </u>
	SALVEMINI, D., et al., "A Nonpeptidyl Mimic of Superoxide	
	Dismutase with Therapeutic Activity in Rats," 286: 304-306, 8	
	October 1999, 306 (Amer. Assoc. for Adv. Sci. 1999).	<u> </u>
	HOLMER, A.F., "Researchers Are Testing 402 New Medicines for	
	Cancer," 2001 Survey, New Medicines in Development for Cancer,	
	p. 1-56, (Pharmaceutical Research Manufacturers America 2001).	_
8	VOZIYAN, PAUL A., et al., "Mechanism of Farnesol Cytotoxicity:	
166	Further Evidence for the Role of PKC-Dependent Signal	<u> </u>
<del></del>		

Examiner signature	1	3/18/103
	10 40	•

Sheet 3 of 9

APR 2 6 2002

OTHER PRIOR ARTENT LITERATURE DOCUMENTS

			Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	Т	l
ı	Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of field, date, page, vor issue, passes,	•	ı
	2244		city and /or country where published		۱
	Initials	No.	etty and for country where published		J
	111111413	1,01			

$\Omega_{a}$	Transduction in Farnesol-Induced Apoptotic Cell Death,"	
	Biochemical and Biophysical Research Communication, 212(2):	
0 /	479-486, July 17, 1995 (Academic Press 1995).	4
1	BOUNOUS, GUSTAVO, "Whey Protein Concentrate (WPC) and	
	Glutathione Modulation in Cancer Treatment," Anticancer Research	
/	20: 4785-4792 (2000).	_
	McINTOSH, GRAEME H., et al., "Dairy Proteins Protect against	
	Dimethylhydrazine-Induced Intestinal Cancers in Rats,"	
	[Biochemical and Molecular Roles of Nutrients] J. Nutrition	
	125(4):809-816 (Amer. Inst. Of Nutrition 1995).	
	HAKKAK, REZA, et al., "Diets Containing Whey Proteins or Soy	
	Protein Isolate Protect against 7,12-Dimethylbenz(a)anthracene-	
	induced Mammary Tumors in Female Rats," Cancer Epidemiology,	-
1 / 1	Biomarkers & Prevention 9: 113-117, January 2000.	
	BOUNOUS, GUSTAVO, "Dietary Whey Protein Inhibits the	
	Development of Dimethyl-Hydrazine Induced Malignancy,"	
1 / 1	Clinical and Investigative Medicine, 11(3): 213-217 (Univ. of	
	Toronto Press 1988).	
	McADAM, B. F., et al., "Systemic biosynthesis of prostacyclin by	
	cyclooxygenase (COX)-2: The human pharmacology of a selective	
1/	inhibitor of COX-2," Proc. Natl. Acad. Sci. USA, 96: 272-277,	
	January 1999 (Nat'l. Acad. Of Sci. 1999).	
	BECKMANN-KNOPP, SVANE, et al., "Inhibitory Effects of	
	Silibinin on Cytochrome P-450 Enzymes in Human Liver	
	Microsomes," Pharmacology & Toxicology, 2000, 86: 250-256	
	(Pharmacology & Toxicology 2000).	
	ZI, XIAOLIN, et al., "Modulation of Mitogen-Activated Protein	
	Kinase Activation and Cell Cycle Regulators by the Potent Skin	
1 \ 1	Cancer Preventive Agent Silymarin," Biochemical and Biophysical	ı
	Research Communications 263: 528-536 (Academic Press 1999).	
1	ZHAO, JIFU, et al., "Inhibitory effect of a flavonoid antioxidant	
1/1	silymarin on benzoyl peroxide-induced tumor promotion, oxidative	
	stress and inflammatory responses in SENCAR mouse skin,"	
1 2	Carcinogenesis, 21(4): 811-816 (Oxford University Press 2000).	
95	JIANG, CHENG, et al., "Anti-Angiogenic Potential of a Cancer	L

Biomisian 10000	
Examiner 3/1/2/3	)
signature   C	

Sheet 4 of 9

APR 2 6 2002

10/00711	,足,
Appl. No09/997,4	F
Filing Date	計
First Named Inventor: Kindne	ss
Group Art Unit:	69
Examiner Name:	은
Atty Docket No.	13

OTHER PRIOR ART ROSMO ATENT LITERATURE DOCUMENTS

٢	Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	T	1
	Initials	No.	city and /or country where published		

	Chemopreventive Flavonoid Antioxidant, Silymarin: Inhibition of	
	Key Attributes of Vascular Endothelial Cells and Angiogenic	
$ \mathcal{D} $	Cytokine Secretion by Cancer Epithelial Cells," Biochemical and	
7	Biophysical Research Communications 276: 371-378 (Academic	
	Press 2000).	
	SCHRIEWER H., "The effect of silybin dihemisuccinate on	
1 ( )	cholesterol biosynthesis in rat liver homogenates,"	
	Arzneimittelforschung/Drug Research 1977;27(9):1691-4, Abstract,	
	PMID: 579140.	
	SCHRIEWER, VON H., et al., "Die Wirkung von Silybin-	
1 1	dihemisuccinat auf die Cholesterinbiosynthese in	
	Rattenleberhomogenaten," ArzneimForsch. Drug Res. 27 (II), Nr.	
1 )	9 (1977) (Full article, German and English (no translation).	
	WAGNER et al, Zur Chemie und Analytik von Silymarin aus	
	Silybum marianuym Gaertn., Arzneim-Forsch./Drug Res. 24 (4),	
	(1974) 466-471. (Full article, German and English (no translation).	
	BOKEMEYER, C., et al., "Silibinin protects against cisplatin-	
	induced nephrotoxicity without compromising cisplatin or	
	ifosfamide anti-tumor activity," British Journal of Cancer (1996) 74,	
	2036-2041(Stockton Press 1996).	
	SCHULTZ, H. U., et al., "Untersuchungen zum	
	Freisetzungsverhalten and zur Bioäfquivalenz von Silymarin-	
	Präparaten," Arzneim-Forsch./Drug Res. 45 (I), Nr. 1 (1995) 61-64.	
	SHARMA DK, et al., "Hypolipidemic, anti-inflammatory, and	
1 1 1	antineoplastic activity and cytotoxicity of flavonolignans isolated	
	from Hydnocarpus wightiana seeds," J. Nat Prod 1991 Sept-Oct;	
	54(5):1298-302, Nat'l Lib. Of Medicine, PMID: 1800632	
	(Abstract).	
1 / 1	HAKOVA, H., et al., "The effect of silymarin and gamma radiation	
1 \	on nucleic acids in rat organs," J. Pharm. Pharmacol. (1993) 45:	
1	910-912.	
1 2 1	BARTHOLOMAEUS, A.R., et al., "Inhibition of rat liver cytosolic	
L'EN	glutathione S-transferase by silybin," Xenobiotica, 1994, Vol. 24,	

Examiner	MA		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	er a jedine.	ی	1/4/20
signature //	1/	U. S. C.	7.7		15	117 10)
		1 X 1 2 2				

Sheet 5 of 9

APR 2 6 2002

Appl. No. 09/ Filing Date

First Named Inventor: Kindness

Group Art Unit: Examiner Name:

Atty. Docket No.

OTHER PRIOR ART-NON PATEN TERATURE DOCUMENTS

Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	T
Initials	No.	city and /or country where published	L

B	N. 1 17 24 (Texter 9, Ferraig Ltd. 1004)	
(1)	No. 1, 17-24 (Taylor & Francis Ltd. 1994).	_
1	FIEBRICH F., et al., "Silymarin, an inhibitor of prostaglandin	
	synthetase," Experientia 1979 35(2) p. 1550-1552.	
	RYU, HEE-SUG, et al., "High Cyclooxygenase-2 Expression in	
	Stage 1B Cervical Cancer with Lymph Node Metastasis or	
	Parametrial Invasion," Gynecologic Oncology 76, 320-325	
	(Academic Press 2000).	
	HUTCHINS, ANDREA M., et al., "Acetyl-CoA Synthetases I and II	
	from Pyrococcus furiosus." Methods in Enzymology, Vol. 331,	
	(2001) pp. 158 – 167 (Academic Press 2001).	
	SHARMA, D.K., et al., "Hypolipidemic, Anti-Inflammatory, and	
	Antineoplastic Activity and Cytotoxicity of Flavonolignans Isolated	
	from Hydnocarpus Weightiana Seeds," Journal of Natural Products,	
	Vol. 54, No. 5, pp. 1298-1302, SeptOct. 1991.	
	MANNA, SUNIL K., et al., "Silymarin Suppresses TNF-Induced	
	Activation of NF-kB, c-Jun N-Terminal Kinase, and Apoptosis," J.	
\	of Immunology 163: pp. 6800-6809 (The American Association of	
	Immunologists 1999).	
<del>                                     </del>	KIM, HYUN JU, et al., "Protection of Rat Liver Microsomes	П
	against Carbon Tetrachloride-Induced Lipid Peroxidation by Red	1
1 1 1	Ginseng Saponin through Cytochrome P450 Inhibition," Planta	Ì
	Medica 63 (1997) 415-418 (Georg Thieme Verlag Stuttgart/New	Ì
	York 1997).	İ
	GAFFNEY, DAVID K., et al., "Elevated Cyclooxygenase-2	
	Expression Correlates with Diminished Survival in Carcinoma of	
	the Cervix treated with Radiotherapy," Int. J. Radiation Oncology	
	Biol. Phys., Vol. 49, No. 5, pp. 1213-1217, (Elsievier 2001).	
<del>                                     </del>	WONG, BRADLEY K., et al., "PSA-Specific and Non-PSA	+
	Specific Conversation of a PSA-Targeted Peptide Conjugate of	
	Doxorubicin to its Active Metabolites," Drug Metabolism and	
	Disposition 29(3): 313-318 (2001) (The American Society for	
1	Pharmacology and Experimental Therapuetics 2001).	╁
$ \mathcal{O}_{\alpha} $	NELSON, ANN C., et al., "Variables in Human Liver Microsome	
10/	Preparation: Impact on the Kinetics of L-a-Acetylmethadol	

Examiner signature Smm	3/15/25

Sheet 6 of 9

APR 2 6 2002

Appl. No. O9/97/1017

Filing Date CFIrst Named Inventor: Kind CFIF

Group Art Unit: Examiner Name: Atty. Docket No.

OTHER PRIOR ART-NOW PAPERT LITERATURE DOCUMENTS

		the fitter date page volcissue publisher,	T	ı
Framinar	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	- 1	ı
		city and /or country where published		j
Initials	No.	City and the city and city		

	(LAAM) N-Demethylation and Dextromethorphan O-	
0	Domethylation "Drug Metabolism and Disposition, 29: 319-313	
	(2001), (The American Society for Pharmacology and Experimental	
	Therapeutics 2001).	_
<del></del>	CRUZ, TORCUATA, et al., "Effects of Silymarin on the Acute	
/ /	Stage of the Trinitrobenzenesulphonic Acid Model of Rat Colitis,"	
	Planta Med 67(1) (Feb. 6, 2001) 94-96 (Georg Thieme Verlag	
1 1	Planta Med 6/(1) (Feb. 6, 2001) 94-90 (Georg Thiering Verlage)	
	Stuttgart/New York 2001).	_
	RUDRA, PARVEEN K., et al., "Cell-Specific Enhancement of	
	Doxorubicin Toxicity in Human Tumour Cells by Docosahexaenoic	
[ ]	Acid," Anticancer Research 21: 29-38 (2001).	_
	DRADBIRY C MATTHEW, et al., "Increased Activator Protein 1	
	Activity as Well as Resistance to Heat-induced Radiosensitization,	
	Hydrogen Peroxide and Cisplatin Are Inhibited by Indomethacili iii	
	Oxidative Stress-resistant Cells," Cancer Research 61, 3486-3492,	
	April 15, 2001 (Cancer Research 2001).	_
<del>  </del>	71 YIAOI IN et al "Novel Cancer Chemopreventive Effects of a	
	Flavonoid Antioxidant Silymarin: Inhibition of mRNA Expression	
	of an Endogenous Tumor Promoter TNFa," Biochemical and	
1 1	Biophysical Research Communications 239, 334-339 (Academic	
1 1	Press 1997).	_
<u> </u>	XU, MEI FENG, et al., "Effects by doxorubicin on the myocardium	
	are mediated by oxygen free radicals," Life Sciences 68(8) (Jan. 12,	
	are mediated by oxygen nec radicals, End bottom	í
	2001) 889-901 (Elsievier 2001).	Γ
	RASO, GIUSEPPINA MATTACE, et al., "Inhibition of inducible	
	nitric oxide synthase and cyclooxygenase-2 expression by	
	flavonoids in macrophage J774A.1," Life Sciences 68(8) (Jan. 12,	l
1 1	2001) 921-931 (Elsevier 2001).	┝
	UCAR, MEMDUH, et al., "HMG-CoA Reductase Inhibitors and	١
	Myotoxicity," Review Article; Drug Safety 2000 Jun. 22(0): 4412	
	457 (Adis International Limited 2000).	╀
<del>                                      </del>	FARMER JOHN A., et al., "Comparative Tolerability of the HMG-	l
(	CoA Reductase Inhibitors," Review Article, Drug Safety 2000 Sept.	١
1	23(3) 197-213 (Adis International Limited 2000).	1
1	WHITTLE, B. J. R., "COX-1 and COX-2 products in the gut:	1

•		
Examiner	Marin	3/18/0}
signature		

INFORMATIC	N I	OISC	LOSU	JRE
STATEMENT	BY	APP	LICA	NF

Sheet 7 of 9

OFFICE 3

Appl. No

Filing D:
First Named Inventor: Kindness

Group Art Unit:
Examiner Name:
Atty. Docket No.

OTHER PRIOR ART-NON PATERON LITERATURE DOCUMENTS

Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	T	ĺ
Initials	No.	city and /or country where published	<u> </u>	

a	therapeutic impact of COX-2 inhibitors," GUT, An International Journal of Gastroenterology and Hepatology, Volume 47(3) 1
~ /	September 2000, pp. 320-325 (Gut 2000).
	JACKSON, LUCINA M., et al., "COX-2 Selective Nonsteroidal
(	Anti-Inflammatory Drugs, Do They Really Offer Any Advantage?"
	Leading Article, Drug 2000 Jun, 59(6) 1207-1216 (Adis
1 1 1	International Limited 2000).
	ATTIGA, FADWA A., et al., "Inhibitors of Prostaglandin Synthesis
1 \	Inhibit Human Prostate Tumor Cell Invasiveness and Reduce the
1 1 1	Release of Matrix Metalloproteinases," Cancer Research 60, 4629-
	4637, August 15, 2000.
	HSU, AO-LIN, et al., "The Cyclooxygenase-2 Inhibitor Celecoxib
1 / 1	Induces Apoptosis by Blocking Akt Activation in Human Prostate
	Cancer Cells Independently of Bcl-2", The Journal of Biological
	Chemistry, 275(5): 11397-11403, April 14, 2000 (Amer. Socy. For
	Biochemistry and Molecular Biology, Inc. 2000.
	TALLY, JOHN J., et al., "4-[5-Methyl-3-phenylisoxazol-4-yl]-
	benzeneusulfonamide, Valdecoxib: A Potent and Selective Inhibitor
	of COX-2," J. Med. Chem, 2000, 43: 775-777 (Amer. Chem. Socy.
1 1 1	2000)
1-1-1	TALLY, JOHN J., et al., "N-[[(5-Methyl-3-phenylisoxazol-4-yl)-
1 1 1	
1 } }	phenyl]sulfonyl]propanamide, Sodium Salt, Parecoxib Sodium: A
1 / 1	Potent and Selective Inhibitor of COX-2 for Parenteral
1.1.1	Administration," J. Med. Chem. 2000, 43: 1661-1663 (Amer. Chem.
	Socy. 2000).
	DEQUEKER, J., et al., "Improvement in Gastrointestinal
	Tolerability of the Selective Cyclooxygenase (COX)-2 Inhibitor,
	Meloxicam, Compared with Piroxicam: Results of the Safety and
	Efficacy Large-Scale Evaluation of COX-Inhibiting Therapies
1 ( 1	(Select) Trial in Osteoarthritis," British Journal of Rheumatology
<b> </b>	1998; 37:946-951 (Brit. Socy. For Rheumatology 1998).
'_	MITCHELL, JANE A., et al., "Cyclo-oxygenase-2: pharmacology,
$ \Omega $	physiology, biochemistry and relevance to NSAID therapy," British
16/1	Journal of Pharmacology (1999) 128: 1121-1132 (Stockton Press
	1999).

Examiner signature	3(12/02

Sheet 8 of 9



# OTHER PRIOR ART-NON PATENT LITERATURE DOCUMENTS

Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	T
Initials	No.	city and /or country where published	

	HUNT, JOHN T., et al., "Discovery of (R)-7-Cyano-2, 3, 4, 5-
	tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-
<i>[</i> ]	thienylsulfonyl)-1H-1,4-benzodiazepine (BMS-214662), a
	Farnesyltransferase Inhibitor with Potent Preclinical Antitumor
	Activity," Journal of Medicinal Chemistry, 43(20): 3587-94,
j	October 5, 2000 (Amer. Chem. Socy. 2000).
	ZAMZAMI, NAOUFAL, et al., "Quantitation of Mitochondrial
	Transmembrane Potential in Cells and in Isolated Mitochondria,"
\	(Mitochondria and Apothosis), Methods in Enzymology 322: 208-
	213 (Academic Press 2000).
	ELLERBY, LISA M., et al., "Measurement of Cellular Oxidation,
	Relative Oxygen Species, and Antioxidant Enzymes During
	Apoptosis," Methods in Enzymology 322: 413-433 (Academic Press
	2000).
	DING, XIAN-ZHONG, et al., "Blockage of Cyclooxygenase-2
1 ./ 1	Inhibits Proliferation and Induces Apoptosis in Human Pancreatic
	Cancer Cells," Anticancer Research 20: 2655-2632 (2000).
	Inhibiting COX-2, A New Discovery to Prevent Breast Cancer,
	American Institute for Cancer Research, NEWSLETTER, Spring
	2001, Issue 71, page 10 (Amer. Inst. For Cancer Research 2001).
	GOLDEN, BRIAN D., et al., "Selective Cyclooxygenase-2,"
	Osteoarthritis, 25(2) 359-378 May 1999 (Rheumatic Disease Clinics
	of North America 1999).
1 / 1	WILLIAMS, CHRISTOPHER, et al., "The Role of COX-2 in
	Intestinal Cancer," Annals New York Academy of Sciences 889: 72-
	83 (NY Acad of Sci. 1999).
	MASFERRER, JAIME L., et al., "COX-2 Inhibitors – A New Class
/	of Antiangiogenic Agents," Annals New York Academy of Sciences
h	889: 84-86 (NY Acad of Sci. 1999).
]	YERGEY, JAMES A., et al., "In Vitro Metabolism of the COX-2 In
	hibitor DFU, Including a Novel Glutathione Adduct
	Rearomatization," Drug Metabolism and Disposition 29(5): 638-644
	(The American Society for Pharmacology and Experimental
	Therapeutics 2001).
LM	EDWARDS, PETER A., et al., "Sterols and Isoprenoids: Signaling

		10.			
Examiner .		7000		 0 1 14	<del> </del>
signature	///		*	12/12/	DZ
signature		P 44.5		1711/47	\(\frac{1}{2}\)
	<b>-</b> ,			 	

INFORMATION	DISCLOSURE
CTATEMENT D	V ADDI ICANT

Sheet 9 of 9

Appl. No. Filing Date 

TERATURE DOCUMENTS

OTHER PRIOR ART-NON CATALOG

Antitude 1.00	Examiner Initials		Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher, city and /or country where published	T	
---------------	----------------------	--	--	---	--

B	Molecules Derived from the Cholesterol Biosynthetic Pathway," Annu. Rev. Biochem. 1999, 68: 157-185 (Annual Reviews 1999).  PETERSON, JEFFREY D., et al., "Glutathione Levels in Antigen-Presenting Cells Modulate Th1 Versus Th2 Response Patterns," Proc. Natl. Acad. Sci. USA 95: 3071-3076, March 1998 (Nat'l Acad. Of Sciences 1998).	
	INOUE, IKUNO, et al., "Lipophilic HMG-CoA reductase inhibitor has an anti-inflammatory effect Reduction of MRNA levels of interleukin-1B, interleukin-6, cyclooxygenase-2, and p22phox by regulation of peroxisome proliferator-activated receptor a (PPARa) in primary endothelial cells," Life Sciences 67 (2000) 863-875 (Elsevier 2000).	
B	WILLOUGHBY, DEREK, A., et al., "COX-1, COX-2, and COX-3 and the Future Treatment of Chronic Inflammatory Disease," The Lancet Ltd., 2000, 355(9204): 646-648, 19 February 2000 (Brity. Med. Socy. 2000).	

Examiner signature

Sheet



PTC/SB/08A (08-00)
Approved for the through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

MB controknumber.

Under the Paperwork Reduction Act of 1995, no persons are required to res	pond to a collection of information unless it contains a yalid O
Substitute for form 1449A/PTO	Complete if Known

# **INFORMATION DISCLOSURE** STATEMENT BY APPLICANT

(use as many sheets as necessary)

of

<del></del> .	
Application Number	09/997,490
iling Date	7 nov 2001
irst Named Inventor	1 4
Group Art Unit	KINDNESS
xaminer Name	1614

Attorney Docket Number

other nubl

(other pub

<del>-  </del>				other publ. 10 she	ets	
				U.S. PATENT DOC	UMENTS	8
Examine	Cite	U.S. Patent		Name of Patentee or Applicant	Date of Publication of	Pages, Columns, Lines, Where Relevant
Initials*	No.1	Number	(if known)	of Cited Document	Cited Document MM-DD-YYYY	Passages or Relevant  Figures Appear
$\triangleleft \square$	ļ	6245797		Winokur	*	
<u> </u>	ļ	6136804		Nichtberger	10/24/ 2000	
$\rightarrow$	↓	4231938		Monaghan	11-04-1980	
	<b>↓</b>	4444784		Hoffman	04-24-1984	
$\vdash$	<b> </b>	4346227		Terahara '	04-24-1982	
	ļ	5273995		Roth	12-28-1993	
1	<del> </del>	<del>5177080</del>		Angerbauer	01-05-1993	
		5354772		Kathawala	10-11-1994	,
D'		5747459		Rowe	05-05-1998	
1	ļ	5888552		Bounous	03-30-1999	
<u> </u>	<del> </del>				<del> </del>	
				<u> </u>	<del>                                     </del>	
·	<u> </u>		_			
<b> </b>					·	
	<b> </b>					
					<del>-   </del>	

				FOR	EIGN PATENT DOCUMENT	rs			
Examiner Initials	Cite No. <sup>1</sup>	Office <sup>3</sup>	Foreign Patent Do	ocument Kind Code <sup>s</sup> (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Te	
<u> </u>	-	WO	99/20110		Winokur	1999			
		wo	09641645		Isakson	12-27-1996		T	
		$oxed{oxed}$	filed as P	CT US 95	/09905			$\top$	
9		wo	00/031120		Kozhemyakin	2000			
		<u></u> ₹	led as PCT	/RU99/00				ļ	
			<del></del>					$oxed{\Box}$	
		1	·····				· ·-·	┼	

Examiner Date 5/	7
	/ ^ 2
Signature Considered 3/18	/ U_
Considered 9/10/	_

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U. S. Patent and Trademark Office, Washington, DC 20231.

DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

<sup>&</sup>lt;sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

**Sheet** 1 **of** 10

APR 2 6 2002

Appl. No	
Filing Date 27 /7 Nov 20	707
First Named Inventor: Kindness	Ĭ
Group Art Unit:	8
Examiner Name:	$\geq$
Atty. Docket No.	T

OTHER PRIOR ART-NOW ATENT LITERATURE DOCUMENTS

Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	
Initials	No.	city and /or country where published	

M	BAUER G. et al, Reactive Oxygen and Nitrogen Species: Efficient, Selective, and Interactive Signals During Intercellular Induction of Apoptosis; Abteilung Virologie, Institute for Medizinische Mikrobiologie und Hygiene, Universität Freiburg, D-79104 Freiburg, Germany; Anticancer Research 20: 4115-4140 (2000)	
	BOLANOS JP, Nitric Oxide, Mitochondrial Function and Excitotoxicity, Methods Findings Exp. Clin Pharmacol, 22(6): 375-77 (Prous Science 2000)	
	WINK D and MITCHELL J, in "Chemical Biology of Nitric Oxide: Insights into Regulatory, Cytotoxic, and Cytoprotective Mechanisms of Nitric Oxide," Free Radical Biol. & Med. 25(4): 434-456, (Elsevier Sept. 1998)	
	VOGT A et al, "A Non-peptide Mimetic of Ras-CAAX: Selective inhibition of Farnesyl Transferase and Ras Processing," 270(2) J. Biological Chemistry 660-664 (Amer. Society For Biochemistry and Molecular Biology, Inc. Jan. 13, 1995)	
	GUNAWARDENA K et al, "Vitamin E and Other Antioxidants Inhibit Human Prostate Cancer Cells Through Apoptosis," The Prostate 44:287-295 (Wiley-Liss, Inc. 2000)	
	LIU XH et al, "Inhibition of Cyclooxygenase-2 suppresses Angiogenesis and the Growth of Prostate Cancer In Vivo," J. of Urology, 164:820-825 (Amer. Urological Ass'n Sept. 2000)	
	Abstract, MOHAMMED SI et al, "Expression of Cyclooxygenase-2 (COX-2) in Human Invasive Transitional Cell Carcinoma (TCC) of the Urinary Bladder," J. Urology 164:1844-45(Amer. Urological Ass'n Nov. 2000)	
On I	HADDAD J et al, "Thiol Regulation of Pro-Inflammatory Cytokines Reveals a Novel Immunopharmacological Potential of Glutathione in the Alveolar Epithelium" The Journal of Pharmacology and Experimental Therapeutics, Vol. 296, No. 3, pg. 996-1005 (Amer. Socy. For Pharm. And Experimental Therapeutics 2001)	

		4	_	 $\Delta$	_	 2	 	7	
Examiner signature		1	2	V		1		3/14/0	13
	 _								

# Appl. No.\_ Filing Date\_ First Named Inventor: Kindney

Group Art Unit:\_ Examiner Name:\_

**Sheet** 2 **of** 10

INFORMATION DISCLOSURE

STATEMENT BY APPLICANT OF P

Atty. Docket No. ERATURE DOCUMENTS OTHER PRIOR ART-NON PAT

Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	Γ
Initials	No.	city and /or country where published	L

//	FOLKERS, K et al, "Survival of Cancer Patients on Therapy with	
	Coenzyme Q10," Biochemical and Biophysical Research	
	Communications; Vol. 192, No. 1, 1993, April 15, 1993, p. 241-245	
	(Academic Press 1993).	
1 1	CHENG D et al, "Activation of Acyl-Coenzyme A: Cholesterol	
1 / 1	Acyltransferase by Cholesterol or by Oxysterol in a Cell-free	
	System," The Journal of Biological Chemistry; Vol. 270, No. 2,	
\	Issue of January 13, pp. 685-695, (Am. Soc'y. for Biochem. And	
	Molecular Biol. 1995).	
	LY D et al, "Mitotic Misregulation and Human Aging," Science; 31	_
	March 2000; Vol. 287, pg. 2486-2492 (Amer. Assoc for the Adv. Of	
	Sci.)	
	AGARWAL B et al, "Lovastatin Augments Sulindac-Induced	_
1   1	Apoptosis in Colon Cancer Cells and Potentiates Chemopreventive	
	Effects of Sulindac," Gastroenterology 1999; Vol 117:pp.838-847	
1   1	(Amer. Gastroenterological Assoc.)	
<del>                                     </del>	THIBAULT A et al, "Phase I Study of Lovastatin, and Inhibitor of	
	the Mevalonate Pathway, In Patients with Cancer," Clinical Cancer	
	Research; Vol. 2, 483-491, March 1996.	
	JI Yan-Shan, XU Quing, SCHMEDTJE, J, "Hypoxia Induces High-	
	Mobility-Group Protein I(Y) and Transcription of the	
\		
	Cyuclooxygenase-2 Gene in Human Vascular Endothelium,"	
	Circulation Research 83(3): 295-304, Aug. 10, 1998, (Amer. Heart	
	Assoc. 1998)	
	NELSON D and COX M, Lehninger Principles of Biochemistry,	
	(Worth Publishers NY 3 <sup>rd</sup> ed. 2000) see especially pp. 528-542, 810-	
	814, 840-843, 856-859, 1058-1063.	
	SALWAY J, Metabolism at a Glance, (Blackwell Science Oxford	
	London 1999) pp. 12-15, 32-33, 48-51, 60-61, 68-69, 86-89.	
	MORINI M, et al, "The role of the thiol N-acetylcysteine in the	
	prevention of tumor invations and angiogenesis," Int'l J. of	
1	Biological Markers 14(4): 268-271 (Wichtig Editore 1999)	
	RODAN, G and MARTIN J, "Therapeutic Approaches to Bone	
	Diseases," Science 289:1508-1514 (Sept. 1, 2000 Amer. Assoc for	
d	the Adv. Of Sci.)	
<del></del>		

		1
Examiner signature	3/18/	03

**Sheet** 3 **of** 10

Appl. No. 09/997, 4
Filing Date
First Named Inventor: Kind
Group Art Unit:
Examiner Name:
Atty. Docket No.

OTHER PRIOR ART-NON PATERITERATURE DOCUMENTS

Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	T	F
Initials	No.	city and /or country where published		

		$\overline{}$
	GHOSH J and MYERS C, "Inhibition of arachidonate 5-	
	lipoxygenase triggers massive apoptosis in human prostate cancer	
Col	cells," Proc. Nat'l Acad. Sci. USA, 95:13182-13187 (Nat'l Acad.	
	Of Sci. Oct.1998)	
)	SALVUCCI, O., CARSANA, M., BERSANI, I., TRAGNI, G. and	
	JANICHINI, A., "Antiapoptotic Role of Endogenous Nitric Oxide in	
/	Human Melanoma Cells," Cancer Research 61, 318, 326, January 1,	
	2001, (Cancer Research 2001).	
	SUZUKI, Y., KONDO, Y., HIMENO, S., NEMOTO, K.,	
	AKIMOTO, M., and IMURA, N., "Role of Antioxidant Systems in	
	Human Androgen-Independent Prostate Cancer Cells," The Prostate	
	43: 144-149 (2000 Wiley-Liss, Inc.)	
	MADAAN, S., ABEL, P.D., HEWITT, C.R., STOTT, M.A.,	
	STAMP, G.W.H., and LALANI, E.N., "Cytoplasmic induction and	
	over-expression of cyclooxygenase-2 in human prostate cancer:	
	implications for prevention and treatment," BJU International	
	(2000) 736-741 (2000 BJU International)	
	SILVERSTEIN, F., FAICH, G., GOLDSTEIN, J., SIMON L.,	
	PINCUS, T., WHELTON, A., MAKUCH, R., EISEN, G.,	
	AGRAWAL, N., STENSON W., BURR, A., ZHAO, W., KENT, J.,	
	LEFKOWITH, J., VERBURG, K., GEIS, G., "Gastrointestinal	
	Toxicity With Celecoxib vs Nonsteroidal Anti-inflammatory Drugs	
	for Osteoarthritis and Rheumatoid Arthritis – The Class Study: A	
	Randomized Controlled Trial," J. Amer. Med. Assoc., September	
	13, 2000 – Vol. 284, No. 10, 1247 – 1255 (Amer. Med. Assoc.	
	2000)	
	BOIREAU, A., BUDEDAT, P., BORDIER, F., COIMBRA, M.,	$\dashv$
	MEUNIER, M., IMPERATO, A., MOUSSAOUI, S., "Effects of	
	Ebselen, a Glutathione Peroxidase Mimic, in Several Models of	
	Mitochondrial Dysfunction," Annals of NY Acad. Sci. 893: 254 –	
	257 (NY Acad. Of Sci. 2000)	
	YASUDA, H., "Prevention of Neurodegeneration by a	$\dashv$
X -		
149	Neuroprotective Radical Scavenger," Annals NY Acad Sci. 893:	
	430-433 (NY Acad. Of Sci. 2000)	_
	COHEN, G., and KESLER, N., "Monoamine Oxidase Inhibits	

Examiner 3/13/03		
	Examiner / SV V V	3/18/03

# RECEIVEI MAY 0 3 2002

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

city and /or country where published

**Sheet 4 of** 10

No.

**Initials** 

	Appl. No. 0 // ( / /)
	Filing Date
PE	First Named Inventor: Ki
ধু	Group Art Unit:
2 6 2002 8	Examiner Name:
14	Atty. Docket No.
IT I AUTON A	TIDE DOCIMENTS

OTHER PRIOR ART-NON PARTITION PARTITION PARTITION PARTITION PRIOR ART-NON PARTITION PARTITION PARTITION PARTITION PARTITION PRIOR ART-NON PARTITION | 8     | Mitochondrial Respiration Annals NY Acad Sci. 893: 273-278 (NY Acad. Of Sci. 2000). |  |
|-------|---|--|
| 1     | LICHTENSTEIN, D. and WOLFE, M., "COX-2—Selective                                    |  |
|       | NSAIDs New and Improved?," (Editorial) J. Amer. Med. Assoc.,                        |  |
|       | September 13, 2000 – Vol. 284, No. 10, 1297 – 1299 (Amer. Med.                      |  |
|       | Assoc. 2000)  |  |
|       | KIRSCHENBAUM, A., KLAUSNER, A., LEE, R., UNGER, P.,                                 |  |
| )     | YAO, S., LIU, X. and LEVINE, A., "Expression of                                     |  |
|       | Cyclooxygenase-1 and Cyclooxygenase-2 in the Human Prostate,"                       |  |
|       | 2000, Elsevioer Science, In., p. 671-676, (Urology 56 (4) 2000)                     |  |
| 1 1   | GUPTA, S., SRIVASTAVA, M., AHMAD, N., BOSTWICK, D.,                                 |  |
|       | and MUKHTAR, H., "Over-Expression of Cyclooxygenase-2 in                            |  |
|       | Human Prostrate Adenocarcinoma," The Prostate 42:73-789 (2000),                     |  |
|       | (2000 Wiley-Liss, Inc.)   |  |
|       | ABSTRACT- CARSON, J., KULIK, G., and WEBER, M.,                                     |  |
|       | "Antiapoptotic Signaling in LNCaP Prostate Cancer Cells: A                          |  |
| 1 1 1 | Survival Signaling Pathway Independent of Phosphatidylinositol                      |  |
|       | 3'—Kinase and Akt/Protein Kinase B," The Prostate 42:79-80 (2000)                   |  |
|       | Wiley-Liss Inc.)  |  |
|       | SERHAN, C., CLISH, C., BRANNON, J., COLGAN, S., CHIANG,                             |  |
|       | N., and GRONERT, K., "Novel Functional Sets of Lipid-derived                        |  |
|       | Mediators with Antiinflammatory Actions Generated from Omega-3                      |  |
|       | Fatty Acids via Cyclooxygenase 2-Nonsteroidal Antiinflammatory                      |  |
| 1 1 1 | Drugs and Transcellular Processing," J. Exp. Med. Volume 192,                       |  |
|       |   |  |
|       | Number 8, October 16, 2000 1197-1204 (The Rockefeller                               |  |
|       | University Press New York).   |  |
|       | KULKARNI, S., JAIN N., and SINGH, A., "Cyclooxygenase                               |  |
|       | Isoenzymes and Newer Therapeutic Potential for Selective COX-2                      |  |
|       | Inhibitors," Methods Find Exp Clin Pharmacol 2000, 22(5): 291-298                   |  |
| !     | (2000 Prous Science)  |  |
|       | KELLOGG, G., CROWELL J., STEELE, V., LUBET, R. BOONE,                               |  |
|       | CH. MALOLE W., HAWK, E., LIEBERMAN, R., LAWRENCE,                                   |  |
| 1/W   | J., KOPELOVICH, L., ALI, I., VINER, J. and SIGMAN, C.,                              |  |
| 16/   | "Progress in Cancer Chemoprevention", Annals of NY Acad. Sci.,                      |  |
| 1 1 1 | 889: 1-13, (NY Acad. Of Sci. 2000).   |  |

Examiner	A 21 -	2/12/12
signature	m	3/10/03

# RECEIVED

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

**Sheet** 5 **of** 10

APR 2 6 2002

Appl. No. 09 9 9 7, 4 90
Filing Date
First Named Inventor: Kindness
Group Art Unit:
Examiner Name:
Atty. Docket No.

## OTHER PRIOR ART-NON PATER PRIOR | Examiner | Cite | Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher, | T |
|----------|------|---|---|
| Initials | No.  | city and /or country where published  |   |

	EARNSHAW, W., MARTINS, L. and KAUFMANN, S.,
	"Mammalian Caspases: Structure, Activation, Substrates, and
	Functions During Apoptosis," Annual Rev. Biochem 1999 68: 383-
	424 (Annual Reviews (1999)
. /	EDWARDS, P. and ERICSSAON, J., "Sterols and Isoprenoids:
(	Signaling Molecules Derived From the Cholesterol Biosynthetic
	Pathway," Annu. Rev. Biochem. 1999, 68: 157-185 (Annual
	Reviews 1999) (pp. 157-175 attached)
	STRITTMATTER, W. and ROSES, A., "Apolipoprotein e and
	Alzheimer disease," Proc. Natl. Acad. Sci. USA, Vol. 92, pp. 4725-
	4727, May 1995 (Nat'l Acad. Of Sci. 1995)
	OBERLEY, T., ZHONG, W., SZWEDA, and OBERLEY, L.,
	"Localization of Antioxidant Enzymes and Oxidative Damage
	Products in Normal and Malignant Prostate Epithelium," The
	Prostate 44: 144-155 (2000) (2000 Wiley-Liss, Inc.)
	DENKERT, C. KOBEL, M., BERGER, S., SIEGERT, A.,
LECLERE, A., TREFZER, U. and HAUPTMANN, S., "Expressi	
	of Cyclooxygenase 2 in Human Malignant Melanoma," Cancer
	Research 61: 303-308, January 1, 2001.
	CHINERY, R., BEAUCHAMP, R., SHYR, Y., KIRLAND, S.,
	COFFEY, R. and MORROW, J., "Antioxidants Reduce
	Cyclooxygenase-2 Expression, Prostaglandin Production, and
	Proliferation in Colorectal Cancer Cells," Cancer Research 58:
	2323-2327, June 1, 1998.
	RAO, G., TATE, M., MURTHY, M., HEBBEL, R., and WHITE, J.,
	"Influence of Antioxidants on Arachidonic Acid Metabolism and
	Platelet Function," Biochemical Medicine and Metabolic Biology
	51: 74-79 (1994) (Academic Press, Inc.)
	SADKAMOTO, W., FUJIE, K., NISHIHIRA, J., HANDA, H.,
	UEDA, N., and YAMAMOTO, S., "Effect of vitamin E on
expression of cyclooxygenase-2 in lipopolysaccharide-stimulated	
macrophages," Biochimica et Biophysica Acta 1304 (1996) 139-1	
	(Elsevier Science B.V. 1996)
B	PAGLIN, S., HOLLISTER, T., DELOHERY, T., HACKETT, N.,
[ ](	McMAHILL, M., SPHICAS, E., DOMINGO, D., and YAHALOM,

	Examiner signature		3/18/03
--	--------------------	--	---------

**Sheet** 6 **of** 10

	Anni Na	99/997,490
_	Appl. No	<u> </u>
E	Filing Date_	
رمر ر ا		

First Named Inventor: Kind

Group Art Unit:

Atty. Docket No.

OTHER PRIOR ART-NON PATENT EXERATURE DOCUMENTS

<del></del>		
	J., "A Novel Response of Cancer Cells to Radiation Involves	
	Autophagy and Formation of Acidic Vesicles," Cancer Research 61,	
<u> </u>	439-444, January 15, 2001	
1	JOSSE, C., LEGRAND-POELS, S., PIRET, B., SLUSE, F., and	
/	PIETTE, J., "Impairment of the Mitochondrial Electron Chain	
/	Transport Prevents NF-kB Activation by Hydrogen Peroxide," Free	
(	Radical Biology & Medicine, Vol. 25, No. 1, pp. 104-112 (Elsevier	
1 /	Science 1998)	
	CHEN, K., SUH, J., CARR, A., MORROW, J., ZEIND, J., and	
	FREI, B., "Vitamin C suppresses oxidative lipid damage in vivo,	
	even in the presence of iron overload," Am J Physical Endocrinol	
	Metab 279: El406-E1412, 2000 (The American Physiological	
	Society 2000)	
	COFFEY, R., HAWKEY, C., DAMSTRUP, L. GRAVES-DEAL,	
	R., DANIEL, V., DEMPSEY, P., CHINERY, R. KIRKLAND S.,	
	DUBOIS,R. JETTON, T. and MORROW, J., "Epidermal growth	
	factor receptor activation induces nuclear targeting of	
\	cyclooxygenase-2, basolateral release of prostaglandins, and	
	mitogenesis in polarizing colon cancer cells," Proc. Natl. Acad. Sci.	
	USA Col. 94, pp. 657-662, January 1997 (Nat'l Acad. Of Sci.).	
\	MOUTET, M., D'ALESSIO, P., MALETTE, P., DEVAUX, V. and	
	CHAUDIERE, J., "Glutathione Peroxidase Mimics Prevent TNFa-	
	and Neutrophil-Induced Endothelial Alterations," Free Radical	
	Biology & Medicine Vol. 25, No. 3, pp. 270-280(Elsevier 1998)	
	LANDINO, L., CREWS, B., TIMMONS, M., MORROW, J., and	
	MARNETT, L., "Peroxynitrite, the coupling product of nitric oxide	
	and superoxide, activates prostaglandin biosynthesis," Proc. Natl.	
	Acad. Sci. USA; Vol. 93, pp. 15069-15074, December 1996 (Nat'1	
	Acad. Of Science)	
}	Zi X and AGARWAL R, "Novel cancer chemopreventive effects of	
	a flavonoid antioxidant silymarin: inhibition of mRNA expression	
of an endogenous tumor promoter TNF alpha," Biochem. Biophys.		
Res. Commun. 239(1):334-9 Oct. 9 1997 (abstract NAT'L LIB. OF		
4	MED. PUBMED PMID 9345320)	
6	VALENZUELA A and GARRIDO A, "Biochemical bases of the	

Examiner signature	3/18/03

**Sheet** 7 **of** 10

**Initials** 

Appl. No. Filing Date First Named Inventor: Kindness **Group Art Unit:** Examiner Name: Atty. Docket No. ATURE DOCUMENTS

OTHER PRIOR ART-NON

Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher, Cite Examiner city and /or country where published No.

		_
	pharmacological action of the flavonoid silymarin and of its	
<i>  h</i>	structural isomer silibinin," Biol Res. 27(2): 105-112 (1994)	
0/	Abstract NAT'L LIB. OF MED. PUBMED PMID: 8640239	
	FOSSLIEN E, "Biochemistry of Cyclooxygenase (COX)-2	
	Inhibitors and Molecular Pathology of CIX-2 in Neoplasia," Crit.	
	Rev. in Clin. Labor. Sci. 37(5):431-502 (CRC Press LLC 2000)	
(	[footnotes at pp. 487-502 omitted]	
<del>                                     </del>	CHUNG L W K, ISAACS W and SIMONS, J (editors), "Prostate	
/	Cancer: Biology, genetics, and the New Therapeutics," ch. 21 by	
(	Brooks J and Nelson W, "Chemoprevention of Prostate Cancer," pp.	
	365-375 (Humana Press Totowa NJ 2001)	
<del>                                     </del>	SAMBONGI Y et al, "Mechanical Rotation of the c Subunit	-
	Oligomer in ATP Synthase (F0/F1): Direct Observation," Science	
	286: 1722-1724, Nov 26, 1999 (Nat'l Acad. Of Sci. 1999)	
<del>                                     </del>	CHAURET et al, "In vitro metabolism considerations, including	_
	activity testing of metabolites, in the discovery and selection of the	
	COX-2 inhibitor etoricoxib (MK-0663)" Bioorg. Med. Chem. Lett.	
	11(8): 1059-62, Apr. 23, 2001 (Abstract NAT'L LIB. OF MED.	
	PUBMED PMID 11327589)	_
	Nat'l Cancer Institute, "Interleukin-12 in Treating Patients with	
	Refractory Advanced-Stage Ovarian Cancer or Abdominal Cancer,"	
	Study recruiting patients from www.clinical trials.gov, NLM ID	
	NCT00003439 Jan. 1, 2001 last update	
	Nat'l Cancer Institute, "R115777 in Treating Patients with	1
	Progressive, Metastatic Prostate Cancer that has no responded to	
	Hormone Therapy," Study recruiting patients from www.clinical	
\	trials.gov, NLM ID NCT00005848 Aug. 1, 2000 last update	
	HONG SH et al, "Relationship of arachidonic acid metabolizing	
	enzyme expression in epithelial cancer cell lines to the growth effect	
\	of selective biochemical inhibitors," Cancer Research 59(9):2223-	
	28, May 1, 1999 Abstract NAT'L LIB. OF MED. PUBMED PMID	İ
	10233261.	
	TONG M, "Induction of NAD (+) linked 15-hydroxyprostaglandin	
	dehydrogenase expression by androgens in human prostate cancer	
16/	cells," Biochem. Biophys. Res. Commun. 276(1): 77-81 (Sep. 16	
	cons, Dioenem. Diophys. Res. Commun. 270(1). 77-01 (Bep. 10	

**Sheet** 8 **of** 10

MATION DISCLOSURE	Appl. No. 09/997, 490	エ
EMENT BY APPLICANT	OIP Filing Date 2	= 17
	First Named Inventor: Kindness	夏(
<b>8 of</b> 10	APR 2 6 2002 Sproup Art Unit:	0
	xaminer Name:	တ
	Atty. Docket No.	2007
OTHER PRIOR ART-NON PAT	TENT ETTENATURE DOCUMENTS	

Examiner	Cite	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher,	T
Initials	No.	city and /or country where published	

B	2000) Abstract NAT'L LIB. OF MED. PUBMED PMID 11006085	
<del>                                     </del>	MASFERRER JL et al, "Antiangiogenic and antitumor activities of	
	cyclooxygenase-2 inhibitors," Cancer Research 60(5): 1306-11,	
/	March 1, 2000 Abstract (NAT'L LIB. OF MED. PUBMED	
<del>- (-   -</del>	PMID:10728691).	_
\ \	NOHL H et al, "Antioxidant-derived prooxidant formation from	
	ubiquinol," Free Radical Biol. & Med. 25(6): 666-675 (Elsevier	
	Science 1998)	
)	TSUCHIDA S, Critical Reviews in Biochem. And Molecular Biol.	
	27(4,5): 337-384 (CRC Press Inc. 1992) (attached are pages 337-38,	
	342-343, 355-365).	
	HEBER, D et al, "Cholesterol-lowering effects of a proprietary	
	Chinese red-yeast-rice dietary supplement, Am. J. Clin. Nutr. 69(2):	
	231-6 Feb. 1999. Abstract NAT'L LIB. OF MED. PUBMED PMID	
	9989865	
	SKOTTOVA N et al, "Silymarin as a Potential	
	Hypocholesterolaemic Drug," Physiol. Re. 47:1-7 (1998) (Inst. Of	
	Phys., Acad. Of Sci. Czech Republic, Prague 1997).	
	DEMHLOW C, "Scavenging of Reactive Oxygen Species and	
/	Inhibition of Arachidonic Acid Metabolism by Silibinin in Human	
	Cells," Life Sciences 58(18): 1591-1600 (Elsevier Science Inc.	
	1996)pp. 1591-99 attached.	
	ZHAO J and AGARWAL R, "Tissue distribution of silibinin, the	
	major active constituent of silymarin, in mice and its association	
	with enhancement of phase II enzymes: implications in cancer	
	chemoprevention," Carcinogenesis 20(11):2101-2108 (Oxford	
	University Press 1999)	
-\	AGARWAL R et al, "Inhibitory effect of silymarin, an anti-	$\dashv$
\	hepatoxic flavonoid, on 12-O-tetradeconoylphorbol-13-acetate-	
\	induced epidermal ornithine decarboxylase activity and mRNA in	
	SENCAR mice," Carcinogenesis 15(6):1099-1103 (Oxford	
\	University Press 1994)	
<del></del>	BHATIA N et al, "Inhibition of human carcinoma cell growth and	$\dashv$
$\alpha$	DNA synthesis by silibinin, an active constituent of milk thistle:	
X/		
	comparison with silymarin," Cancer Letters 147 (1999): 77-84	$\Box$

Examiner signature	3/18/03

**Sheet** 9 **of** 10

Appl. No. Filing Date First Named Inventor: Kindness Group Art Unit: Examiner Name: Atty. Docket No.

URE DOCUMENTS

OTHER PRIOR ART-NON PA

Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher, Cite **Examiner** city and /or country where published No. **Initials** 

	(Elsevier Science Ireland Ltd. 1999)	
1/2	SOSLOW et al, "COX-2 is expressed in human pulmonary, colonic,	
6)	and mammary tumors," 89(12): 2637-2645 (Dec. 15, 2000)	
1 1	(American Cancer Socy. 2000)	
	MILLER T et al, "5-HETE Congeners as Modulators of cell	
(	proliferation," Bioorg Med. Chem. Lett. 10(17):1913-16 (Sep. 4,	
	2000) abstract NAT'L LIB. OF MED. PUBMED PMID 10987416.	
/	ZHAO J et al, "Significant inhibition by the flavonoid antioxidant	
	silymarin against 12-O-tetradeconoylphorbol-13-acetate-caused	
/	modulation of antioxidant and inflammatory enzymes, and	
	cyclooxygenase 2 and interleukin-1 alpha expression in SENCAR	
	mouse epidermis: implications in the prevention of stage I tumor	
	promotion," Mol Carcinog. 26(4):321-333, Dec. 1999 Abstract	
	NAT'L LIB. OF MED. PUBMED PMID 10569809	
	DEHMLOW C, et al, "Scavenging of reactive oxygen species and	
	inhibition of arachidonic acid metabolism by silibinin in human	
	cells," Life Science 58(18): 1591-1600 (1996) Abstract NAT'L	
	LIB. OF MED. PUBMED PMID 8649189	
	YERGEY JA et al, "In vitro metabolism of the COX-2 inhibitor	
	DFU, including a novel glutathione adduct rearomatization," Drug	
	Metab. Dispos. 29(5): 638-44, May 2001 Abstract Nat'l Lib. Of	
	Med. PUBMED PMID 11302928	
	ZI X, "A flavonoid antioxidant, silymarin, inhibits activation of	
	erbB1 signaling and induces cyclin-dependent kinase inhibitors, G1	
	arrest, and anticarcinogenic effects in human prostate carcinoma	
	DU145 cells," Cancer Research, 58(9):1920-29 May 1, 1998	
	(Abstract Nat'l Lib. Of Med. PUBMED PMID 9581834)	
	Abstract and Paper, DHAKSHINAMOORTHY et al, "Antioxidant	
	regulation of genes encoding enzymes that detoxify xenobiotics and	
	carcinogens," 6 <sup>th</sup> Internet World Congress for Biomedical Sciences,	
	www.uclm.es/inabis2000/symposia/ Jan 24, 2000.	
	MANNA SK et al, "Silymarin suppresses TNF-induced activation	
	of NF-kappa B, c-Jun N-terminal kinase, and apoptosis," J. Immunol	
	163(12):6800-09 (Dec. 15, 1999) Abstract Nat'l Lib. Of Med.	
L	PUBMED PMID 10586080	

Examiner signature	m	1	3	1/8/03
				<b>-</b>

**Sheet** 10 **of** 10

Appl. No. 09/997,48	<b>*#</b>
Filing Date	子
First Named Inventor: Kindness	品
Group Art Unit:	<u> </u>
Examiner Name:	$\Xi$
Atty. Docket No.	5
URE DOCUMENTS	2/009

OTHER PRIOR ART-NON PATEN

OTHER PRIOR ART-NON PATER PARTURE DOCUMENTS							
Examiner Initials	Cite No.	Author in CAPITAL LETTERS, title of article, title of item, date, page, vol-issue, publisher, city and /or country where published	Т				

1	RUI YC, "Advances in pharmacological studies of silymarin,"				
1 41	Mem. Inst. Oswaldo Cruz 1991:86 Sup. 2:79-85 Abstract Nat'l Lib.				
	Of Med. PUBMED PMID 1842018				
Í	SPARROW C et al, "Simvastatin has anti-inflammatory and				
	antiatherosclerotic activities independent of plasma cholesterol				
	lowering," Arterioscler. Thromb. Vac. Biol. 21(1): 115-21 (Jan.				
2001) Abstract Nat'l Lib. Of Med. PUBMED PMID 1114594					
	PARMENTIER M, et al, "Regulation of lipopolysaccharide-				
mediated interleukin-1 beta release by N-acetylcysteine in TF					
	cells," Eur. Respir. J. 16(5): 933-39, Nov. 2000 (Abstract Nat'l Lib.				
	Of Med. PUBMED PMID 11153595)				
	HATA S et al, "Synthesis of sterols and 5-lipooxygenase products				
	are required for the G1-S phase transition of interleukin-2-dependent				
1 1	lymphocyte proliferation," Microbiol Immunol. 31(12): 1231-44				
	(1987) (Abstract Nat'l Lib. Of Med. PUBMED PMID 3131638)				
	INOUE I et al, "Lipophilic HMG-CoA reductase inhibitor has an				
	anti-inflammatory effect: reduction of MRNA levels for interleukin				
	1 beta, interleukin-6, cyclooxygenase-2, and p22phox by regulation				
	of peroxisome proliferator-activated receptor alpha (PPARalpha) in				
(	primary endothelial cells," Life Sci. 67(8): 863-76 (Jul 14, 2000)				
\	Abstract Nat'l Lib. Of Med. PUBMED PMID 10946846.				
	BOUNOS G, "Whey Protein Concentrate (WPC) and Glutathione				
1 /h	Modulation in Cancer Treatment, Anticancer Research 20: 4785-				
('/	4792 (2000).				
<del></del>					

	-			
Examiner		00/	)	 3/1/0/12
signature	WV V			1116705

ا الع